Dear Editor:

With great interest we have read the paper by Wolfram et al. (1) on the role of the sodium-dependent intestinal glucose carrier SGLT1 in the uptake of quercetin-3-glucoside. As the authors correctly point out, previous studies have demonstrated only interaction of quercetin-3-glucoside with SGLT1 (2). In their paper, Wolfram et al. (1) have elegantly attempted to prove actual absorption across the brush border membrane of the small intestine by mounting rat jejunum in Ussing-type chambers and exposing this to several inhibitors of SGLT1. A prerequisite of this study design is that the inhibitors chosen indeed inhibit only SGLT1. Unfortunately, this is not the case in their study.

Lactase phloridzin hydrolase (LPH) is an enzyme present in the brush border membrane of the small intestine capable of hydrolyzing quercetin-3-glucoside and thus enabling uptake of quercetin in the small intestine (3). Day et al. (3) have shown that, with purified lamb small intestinal LPH, the lactase site is responsible for 70% of the hydrolysis of quercetin-3-glucoside and the phloridzin site is responsible for 30%. Substrate specificities of SGLT1 and LPH are very similar (4–6), making it likely that in a system where both proteins are present an SGLT1 inhibitor also inhibits LPH. For this reason, α-glucose and phloridzin, two inhibitors of SGLT1 used by Wolfram et al., might not inhibit only SGLT1. Indeed, inhibition of the lactase-active site of LPH by these two compounds has been reported before with a Kᵢ of 11 mmol/L for glucose (7) and 180 μmol/L for phloridzin (8). Note that the concentrations of glucose (10 mmol/L) and phloridzin (100 μmol/L) that were used by Wolfram et al. to inhibit SGLT1 are very close to these reported Kᵢ. Their data for α-glucose and phloridzin may also point to LPH-mediated transport of quercetin-3-glucoside.

In contrast to SGLT1, LPH is a Na⁺-independent transporter that is thought to act by extracellularly hydrolyzing the quercetin glucosides, followed by transfer of the aglycone across the membrane. Therefore, the second experiment that Wolfram et al. have conducted, inhibiting SGLT1 by replacing Na⁺ with choline, seems to be a good strategy. However, there is any evidence, apart from inhibition of SGLT1 by the lack of Na⁺, that the choline that replaces the Na⁺ does not inhibit LPH? Moreover, even if we assume that the Na⁺-free buffer inhibits SGLT1 only, >50% of the disappearance of quercetin-3-glucoside reported remains unexplained.

Apart from that, if we assume that SGLT1 is responsible for the absorption of quercetin-3-glucoside as the intact glycoside, as the authors suggest, intracellular deglycosylation by a broad specificity cytosolic β-glucosidase would be required to explain the finding of free quercetin in the mucosal medium (1). Day et al. (9) have shown that, in contrast to several other flavonoid glucosides including quercetin-4'-glucoside, human small intestinal β-glucosidase can hydrolyze only a small amount of quercetin-3-glucoside at a low rate. Similarly, rat intracellular β-glucosidases are able only to cleave quercetin-3-glucoside at a low rate (10), and the released aglycone is conjugated quickly to form a glucuronide or sulfate (11). Thus, we contend that the appearance of free quercetin in the mucosal medium and the complete absence of any metabolite in the mucosal compartment rather than involvement of SGLT1 reflect the extracellular hydrolysis of quercetin-3-glucoside by LPH. Using very sensitive and specific high performance liquid chromatography coulter methods, we have found no evidence of the presence of intact quercetin-3-glucoside in human plasma (12) or in plasma from the portal vein of rats after in situ perfusion with quercetin-3-glucoside (unpublished data).

Thus, we believe it is impossible to conclude, or for that matter to dismiss, on the basis of the data presented by Wolfram et al. (1) that SGLT1 is involved in the transport of quercetin-3-glucoside across the brush border membrane of the small intestine.

Ilja C. W. Arts
Aloys L. A. Sesink
Peter C. H. Hollman
RIKILT
Wageningen University and Research Centre
6700 AE Wageningen, The Netherlands

Department of Pharmacology and Toxicology
Nijmegen Center for Molecular Life Sciences
6500 HB Nijmegen, The Netherlands

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